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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/065,902	Applicant(s) Tanzi et al.
	Examiner Karen Clemens	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Jan 18, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *2-12* is/are pending in the application.

Of the above, claim(s) *6-8, 11, and 12* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *2-5, 9, and 10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4 and 5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

"A Notice to comply with Sequence rule

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1644, Group 1640, Technology Center 1600.

DETAILED ACTION

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §1.821 through 1.825 for the reason set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide And/Or Amino Acid Sequence Disclosures.

It is noted that a proper sequence listing was submitted on 04/24/98 for this application. However, the CRF diskette appears to have been lost in the process of entry. Consequently, applicant is required to comply with sequence rules by submitting another CRF diskette and a statement saying that said disk is identical to the paper copy submitted on 04/24/98. The Examiner apologizes for any inconvenience.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because the serial number of the provisional application stated in the oath should be 60/044262 and not 06/044262.

4. The specification on page 1 should be amended to correct the serial number of the provisional application.

5. Applicant's submission of the International Search Report on the IDS (Form PTO 1449) Paper No. 5 is acknowledged, however these citations have been crossed out as they are not appropriate for an IDS.

6. Drawings have been submitted which fail to comply with 37 C.F.R. § 1.84. Please see the enclosed form PTO-948.

7. Claims 2-12 are pending in this application.

Election/Restriction

8. Applicant's election without traverse of Group II, claims 2-5 and 9-10 in Paper No. 9 is acknowledged. Claims 6-8 and 11-12 are being withdrawn from further consideration by the Examiner as being drawn to a nonelected invention (*see 37 C.F.R. §1.142(b)*).

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraph of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 2-3 are rejected under 35 U.S.C. 102(a) as being anticipated by Vito et al. (*J. Biol. Chem.* 271(49):31025-31028, 1996).

Vito et al. teach an antibody having specific binding affinity to the carboxyl-terminal end fragment (CTF) of Presenilin 2 (PS2) from which the proteolytically processed 20 kDa PS2 CTF is derived (see page 31025, Experimental Procedures, Antisera Production section in particular). Vito et al. teach the rabbit polyclonal antisera raised against the peptide spanning amino acids Met ^{438}-Ile ^{448} (full length = 448 amino acids) which are identical in both mouse and human PS2. Vito et al. also teach a method of detecting an artificially truncated form of the PS2 CTF, which the 20 kDa fragment encompasses, in a sample by precipitating immunocomplexes between the PS2 CTF and the PS2 CTF-specific antisera. The immunoprecipitated PS2 CTF was further analyzed using SDS-polyacrylamide gel electrophoresis followed by Western Blot detection of the PS2 CTF using an enhanced chemilluminescent detection method (see page 31026, bottom left column and Figure 3 in particular). Enhanced chemiluminescence is a light emitting non-radioactive method for detection of immobilized specific antigen, in this case PS2 CTF bound to the primary (anti-PS2 CTF) antibody, using a secondary antibody conjugated to horseradish peroxidase which is labeled to detect the antigen-bound primary antibody.

Therefore, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 U.S.C. § 103

10. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

A) Claim 4 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Vito et al. (*J. Biol. Chem.* 271(49):31025-31028, 1996) in view of Dalbow et al. (US Patent #4116776, 1978).

Vito et al. have been discussed supra.

Vito et al. do not teach a diagnostic kit comprising the antibody and a conjugate comprising a binding partner and a label. However, the '776 patent teach that an antigen-specific antibody and a conjugate comprising a binding partner of the antibody and a label can be put into a diagnostic kit for the method of detecting the desired antigen in a sample (see column 2, lines 31-53).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to pack the PS2-CTF-specific antibodies and a conjugate with a binding partner and a label taught by Vito et al. into a diagnostic kit as taught by the '776 patent. One having ordinary skill in the art at the time the invention was made would have been motivated to use a diagnostic kit to measure PS2-CTF levels in human patients since diagnostic kits are convenient and can be used in diagnosing the presence of certain pathological conditions as taught by the '776 patent.

B) Claim 5 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Vito et al. (*J. Biol. Chem.* 271(49):31025-31028, 1996) in view of Janeway et al. (*Immunobiology*, New York, Current Biology, 1997)

Vito et al. have been discussed supra.

Vito et al. do not teach a hybridoma which produces the antibody with binding affinity to the PS2-CTF. However, Janeway et al. teach the method of making an antibody-producing hybridoma (see page 2:17, last paragraph in particular). Janeway et al. teach this method as a way to make a limitless supply of a homogeneous antibody with a known specificity. Janeway et al. state that hybridoma-produced monoclonal antibodies have revolutionized the use of antibodies and are now used in most serological assays as diagnostic probes and therapeutic agents (page 2:18, first paragraph in particular).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to produce the PS2-CTF-specific antibodies taught by Vito et al. using hybridoma technology as taught by Janeway et al. One having ordinary skill in the art at the time

the invention was made would have been motivated to produce antibodies using hybridoma's because one could then produce a limitless supply of PS2-CTF specific antibodies which would be useful in a number of serological assays as diagnostic probes and therapeutic agents as taught by Janeway et al.

C) Claims 9-10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tanzi et al. (*Neurobiology of Disease* 3:159-168, 1996) in view of Miller et al. (*Ann. New York Acad. Sci.* 696:133-48, 1993).

Tanzi et al. teach an increase in the accumulation of the PS2-CTF in the detergent-resistant cell fraction of cells with the PS2 mutation, PS2-N141I, a mutation associated with an increased incidence of familial Alzheimer's disease (FAD). Tanzi et al. suggest that these alterations in the processing or degradation of PS2 predate changes in the abnormal secretion of the Beta-Amyloid peptide Aβ (see page 165, column 1 in particular). Tanzi et al. further teach that the deposition of β-amyloid and the excessive accumulation of the Aβ peptide, a major component of β-amyloid, in the brain is believed to play an essential role in the etiology and pathology of Alzheimer's disease (page 159, column 1 in particular).

Tanzi et al. do not teach a method for screening compounds that inhibit the proteolytic processing of presenilin 2 by providing a compound to a cell which processes PS2, measuring the amount of PS2-CTF produced and comparing the amount of PS2-CTF produced in the treated and untreated cell, where the amount of PS2-CTF is decreased as a result of the inhibition of proteolytic processing. Tanzi et al. also do not teach this method using an ELISA assay. However, Miller et al. teach a method of screening compounds that inhibit the proteolytic processing of Interleukin 1β by the cysteine protease, Interleukin β converting enzyme (ICE) (see page 144, Figure 11 in particular). Miller et al. teach the addition of ICE inhibitors to human monocytes, which normally process the 31 kDa IL-1β precursor to the active 17.5 kDa mIL-1β product, followed by the detection of mIL-1β by immunoprecipitation of the plasma with anti-IL-1β antibody. Miller et al. teach the decrease in the presence of 17 kDa proteolytically processed product and an increase in the 31 kDa precursor in cells treated with the ICE protease inhibitors. Miller et al. further teach the measurement of mIL-1β in ICE-inhibitor treated cells using an ELISA assay (see page 145, figure 12 in particular). Miller et al. teach that the ICE-processed IL-1β is closely associated with various inflammatory processes such as leukocyte infiltration, joint swelling and tissue destruction and that IL-1 is an important target of antiinflammatory therapy as demonstrated by the effects of IL-1 antagonists in several animal models of human disease (see page 133 in particular).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to screen compounds that inhibit the proteolytic processing of presenilin 2 using the method taught by Miller et al . One having ordinary skill in the art at the time the invention was made would have been motivated to screen for inhibitors of presenilin 2 processing using the method of Miller et al. because the accumulation of PS2-CTF is believed to be associated with the abnormal accumulation of Aβ, routinely found in Alzheimer's disease

patients, as taught by Tanzi et al. and identifying inhibitors of Presenilin processing could potentially function as a therapeutic agent as taught by Miller et al.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Clemens whose telephone number is (703) 308-8365. The examiner can normally be reached Monday through Friday from 8:00 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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Technology Center 1600
March 27, 2000

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